

## REMARKS

In the Office Action of October 21, 2004, the Examiner states that applicants prior Amendment Under Rule 116 was not entered as a result of the addition of the phrase “synthetic analogs” to the claims. This was deemed by the Examiner to raise new issues. The objectionable language has been omitted from the claims now presented for further examination without intending to surrender any rights in the invention thereby. .

The claims have been amended to clarify that the treatment method of the present invention decreases the formation or growth of plaque on the arterial walls of a mammal. This language is intended as an additional clarification of the term “atherosclerosis”, which has sometimes been confused in the art with the terms “arteriosclerosis” and “thrombosis”. In the context of the present invention, “atherosclerosis” designates a long term, chronic condition resulting from the formation and accumulation of plaque in the arteries over an extended period of time. This contrasts with more acute conditions like thrombosis which are characterized by inflammation and clot formation. Support for this amendment is found on page 4 of the specification.

Since atherosclerosis occurs at the lining of the arterial walls, the claims have also been amended to recite that the P-selectin molecule being inhibited is on endothelial cells which constitute the lining of the arterial walls. As is known to those skilled in the art, the cells which are implicated in thrombosis or ischemia are the platelets which are present in the circulatory system. See the Wagner Declaration Under Rule 132 (“Wagner II Declaration”), enclosed herewith. This amendment is further intended to distinguish over the references which are directed to ischemic events rather than atherosclerosis.

The claims now also recite that the agent is administered repeatedly to the mammal in sequential doses or by controlled release over a period of months or years. This is intended to distinguish over other treatment methods which do not require long term administration. Support for this amendment is found on page 13 of the specification.

Finally, the claims now specify that in the event the agent is a mimetic, the agent must resemble PSGL-1 in shape and charge distribution. Thus, the word “mimetic” is now described in both functional and physical terms. Antecedent support for this amendment is found in the specification at page 11.

The applicants’ general position regarding the inhibition of P-selectin and E-selectin is as follows. Applicants maintain that not all inhibitors of P-selectin also function as inhibitors of E-selectin. Consequently, the mere fact that a reference identifies an agent as an inhibitor of P-selectin does not also mean that the particular agent inhibits E-selectin. In order to determine whether a particular agent is capable of inhibiting both selectins, the inhibitor must be used on both selectins on a trial-and-error basis, and the results must be compared to a standard. This requires experimental effort, and is not an inherent characteristic of the inhibitor.

For examination purposes, applicants hereby elect the “PSGL-1” species for further prosecution on the merits. The Examiner has stated that PSGL-1 analogs read on fragments and chimeric constructs thereof. Applicants reserve the right to request reinstatement of claims having a more generic scope should the elected claims ultimately be found to be allowable.

Claims 71, 81, 87, 88, 89, 92, 94 and 95 are pending and remain in the application. Claims 96 and 97 are newly added. The remaining claims have been canceled without prejudice.

Claims 71-73, 77-81 and 83-90 stand rejected under 35 U.S.C. §102 (e) as being anticipated by Cummings et al. (U.S. Patent No. 5,464,778). Claims 71-73, 77-81 and 83-95 also stand rejected under 35 U.S.C. 103(a) as being obvious over Cummings et al. in view of Larsen et al. (U.S. Patent No. 5,480,679), Tedder et al. (U.S. Patent No. 5,834,425), Coller et al. (U.S. Patent No. 5,976,532), and Sluiter et al. (*Journal of Cardiovascular Pharmacology*, pages S37-S44, 1993). These grounds of rejection are respectfully traversed.

The Cummings et al. reference states that a P-selectin glycoprotein ligand can be used as an inhibitor of P-selectin binding to cells. The Cummings et al. patent is generally directed to the treatment of acute inflammatory conditions, but the patent does mention atherosclerosis in a section labeled “Clinical Applications”. See col. 18, line 33 of the patent. In particular, the Cummings, et al. patent states that atherosclerosis is an example of a pathological condition in

which an inflammatory response may occur, and that the P-selectin glycoprotein ligand can be used to treat such an inflammatory responses. See col. 18, lines 34-53 of the reference.

It is noted that the present claims are directed to the treatment of atherosclerosis, defined as the formation of fibrous plaque on the interior surfaces of arterial walls. This is in contrast to ischemia, which is an acute condition resulting in the restricted flow of blood in the arteries, ultimately resulting in heart attacks or stroke in many affected individuals. Atherosclerosis, in contrast, is a chronic condition requiring a long term treatment protocol.

Atherosclerosis can be diagnosed following treatment for restenosis, which involves the formation of new arterial blockages at the site of an angioplasty or stenting procedure used for the treatment of a thrombosis. Restenosis is typically caused by a thrombosis (blood clot), and the activation and accumulation of platelets and neutrophils in the artery. Thus, both atherosclerosis and restenosis can be treated following a stenting procedure. The difference is that treatment for restenosis is designed to address the immediate problem of preventing a further coronary blockage resulting from the original thrombosis, while treatment for atherosclerosis is designed to prevent long term sustained arterial damage due to additional plaque buildup in the artery.

Anti-thrombosis treatments focus on the prevention of platelet activation and accumulation (clotting). Treatments for preventing a thrombosis, or the reoccurrence of a thrombosis (restenosis), can be directed at inhibiting platelet activation. The platelet is a cell that circulates with the plasma in the circulatory system. This is distinct from the prevention or treatment of atherosclerosis (plaque formation), which occurs on arterial walls, and is a long term condition. Prevention of plaque buildup involves endothelial cells which coat arterial walls. The endothelial cells are treated, according to the method of this invention, by suppressing or inhibiting the P-selectin receptor on such cells. See, in this regard, the Wagner II declaration, enclosed, which explains the difference between treating a subject for a thrombosis, and treatment of atherosclerosis.

The present claims have been amended to clarify that the treatment method of the present invention decreases the formation or growth of plaque in the arteries of a patient. The Cummings et al. reference, in contrast, is directed to the treatment of acute inflammatory

conditions, such as ischemia and reperfusion. See col. 18, line 64 to col. 19, line 13 of the reference. The focus of the reference, in this regard, is the prevention of leukocyte adherence to vascular endothelium. See col. 19, lines 5-10, in particular. With regard to atherosclerosis, the reference makes the following comments, at col. 19, line 64 to col. 20, line 5:

“Platelet-leukocyte interactions are believed to be important in atherosclerosis. Platelets might have a role in recruitment of monocytes into atherosclerotic plaques; the accumulation of monocytes is known to be one of the earliest detectable events during atherogenesis. Rupture of a fully developed plaque may not only lead to platelet deposition and activation and the promotion of thrombus formation, but also the early recruitment of neutrophils to an area of ischemia.”

These comments do not teach or suggest that the reference contemplates the use of PSGL-1 for reducing the formation of arterial plaque. Rather, the reference is directing one skilled in the art to the treatment of thrombus (blood clot) formation. Such treatment would involve the prevention of platelet activation by leukocytes as described elsewhere in the reference. A reduction in plaque formation is not inherent in the treatment of a thrombosis since plaque reduction would require a treatment regime of months or years.

Furthermore, Cummings et al. is directed to the prevention of platelet activation in the circulatory system, rather than the inhibition of endothelial cell binding which is an essential component of atherosclerosis. See, in particular, the Wagner II Declaration, at paragraphs 4, 5 and 6. Thus, one skilled in the art, reading the Cummings et al. reference, would have no expectation that PSGL-1 could be used to reduce plaque formation, and further, that a long term treatment regime would be required to achieve this result.

Notwithstanding the Examiner’s critique of the Wagner Declaration Under Rule 131 (“Wagner I Declaration”), applicants continue to maintain that the Wagner I Declaration is effective in overcoming the Cummings et al. reference by antedating that reference. The Wagner I Declaration demonstrates that the present invention was conceived prior to the effective filing date of the Cummings et al. reference, and was diligently reduced to practice thereafter. Consequently, applicants continue to maintain that the Cummings et al. reference has been effectively antedated, and is therefore not prior art.

The Wagner I Declaration demonstrates that, prior to the effective date of the reference, applicants discovered that the binding of P-selectin and a ligand of P-selectin contributed to the development of atherosclerosis plaque. As a result, applicants deduced that inhibitors of P-selectin can be used to treat atherosclerosis in mammals based on the rôle of P-selectin and/or E-selectin on the pathogenesis of atherosclerosis as claimed in the present application.

The Examiner maintains that the Wagner I Declaration does not disclose the use of PSGL-1 for treating atherosclerosis as presently claimed in this application, and that, for this reason, it is ineffective. In support of this position, the Examiner has cited MPEP 715.03, and the *In re Tanczyn* case disclosed in that section of the MPEP (*In re Tanczyn*, 146 USPQ 298 (CCPA 1965)). However, this general proposition is subject to several exceptions set forth in the MPEP. See, for instance, the more recent case of (*In re Spiller*, 182 USPQ 614 (CCPA 1974)), also cited in MPEP 715.03, which holds that a Rule 131 declaration need not be commensurate in scope with either the rejected claim or the reference disclosure, provided that the declaration establishes possession of the basic inventive concept, with the proviso that the reference itself does not teach the basic inventive concept.

In the present application, PSGL-1 is part of the original class of inhibitors claimed by applicants as part of their invention. The use of a generic inhibitor, rather than the specific inhibitor species PSGL-1, constitutes part of the basic inventive concept originally claimed by applicants. The use of such inhibitors to treat atherosclerosis was conceived by applicants as part of the work described in the Wagner I Declaration. This work involved a knockout mouse model deficient in P-selectin to establish the principal that a reduction in P-selectin level correlates with a reduction in the accumulation of atherosclerotic lesions and plaque. Applicants rightfully conclude that atherosclerosis can thus be treated by a reduction in P-selectin levels through the use of appropriate inhibitors.

Accordingly, applicants submit that Cummings et al. does not anticipate, or render obvious, the claimed invention, and further, that the reference has been effectively antedated by the Wagner I Declaration.

The secondary references, namely Larsen et al., Tedder et al., Coller et al. and Sluiter et al., do not cure the deficiencies of the Cummings et al. primary reference for the following reasons.

Larsen et al., like Cummings et al., does not relate to the treatment of chronic conditions, such as atherosclerosis, but is instead directed to the treatment of inflammatory or acute conditions. Moreover, neither Cummings et al. nor Larsen et al. disclose that a treatment for atherosclerosis can be administered in conjunction with a vessel-corrective technique, as recited in applicant's claims 91-96. Claims 91-96 require the use of surgical procedures as a diagnostic for atherosclerosis.

Coller et al. relates to the treatment of a thrombotic condition using antibodies to GPIIb/IIIa. The present invention, in contrast, relates to the use of PSGL-1, and variants therefore, rather than antibodies. Cummings et al. does not teach the use of vessel corrective techniques, and does not teach the use of antibodies for therapeutic purposes. Consequently, applicants maintain that there is no basis for combining the Coller et al. and Cummings et al. references.

The Sluiter et al. reference has been cited to provide further evidence that one skilled in the art would have targeted the inhibition of P-selectin-mediated events for inhibiting leukocyte adhesion receptors to alleviate tissue damage in cardiovascular diseases. However, although the Sluiter et al. reference mentions P-selectin in a general sense, there is no disclosure in the reference concerning the inhibition of P-selectin binding to the ligand of P-selectin. In fact, the Sluiter et al. reference is actually directed to the possible role of oxygen-derived free radicals in the treatment of inflammation. See the Summary portion of the reference on page S37, and the discussion on page S38. Accordingly, the Sluiter et al. reference does not add to the teachings of Cummings et al.

Claims 71-73, 77-81 and 83-95 also stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting, on the basis of claims 40-41, 45, 49-52, 56, 59-60 and 73-74 of co-pending application Serial no. 09/436,076, and claims 39-88 of co-pending application Serial no. 09/863,642.

Applicants note that this is a provisional obviousness-type double patenting rejection, and therefore it is premature to formulate a detailed response. However, applicants affirm their intention to file a terminal disclaimer to obviate the rejection in the event that the present application is otherwise in condition for allowance.

In view of the aforementioned facts and reasons, the present application is now believed to overcome the remaining rejections in this application, and to be in proper condition for allowance. Accordingly, reconsideration and withdrawal of the rejections, and favorable action on this application, is solicited. The Examiner is invited to contact the undersigned at the telephone number listed below to discuss any matter pertaining to the status of this application.

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Respectfully submitted,  
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